CLAIMS

[Claim(s)]

[Claim 1]Do a medicinal value so by internal use, and a medicinal value is substantially done so by ****** and injection, And this sufficient pharmaceutical preparation for drug content internal use of the administration number of unit to be the medicinal preparation which makes an active principle a drug with which a medicinal value is no longer demonstrated, and derive oral tolerance by repetition administration by injection, Medicinal preparation which consists of this pharmaceutical preparation for drug content injection for prescribing a medicine for the patient after oral tolerance is derived.

[Claim 2]The medicinal preparation according to claim 1 whose drug is a with a molecular weights of 3000 or more protein nature drug.

[Claim 3]The medicinal preparation according to claim 1 or 2 whose injection is intravascular injection, subcutaneous injection, or an intramuscular injection.

[Claim 4]A cure for a disease by this drug do a medicinal value so by internal use, doing a medicinal value so by ****** and injection substantially, and administering orally a drug with which a medicinal value is no longer demonstrated by repetition administration by injection, making oral tolerance derive, and injecting subsequently.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

TECHNICAL FIELD

[Field of the Invention]This invention relates to the medicinal preparation which makes an active principle substantially the drug with which a medicinal value is no longer demonstrated by repetition administration according a medicinal value to ****** and

injection by internal use, concerning medicinal preparation.

PRIOR ART

[Description of the Prior Art]In spite of knowing demonstrating the medicinal value outstanding in the animal experiment, many things which cannot carry out clinical application are in the protein nature drug represented by bioactive peptide. Since many especially protein nature drugs have antigenicity, when a medicine is repeatedly prescribed for the patient by injection of intravenous administration etc., a general immunity response is caused and the moving state in the living body changes a lot. That is, by an antigen-antibody reaction, it disappears promptly and the drug effect maintenance in a long-term therapy becomes difficult from the whole body. There is also a problem of triggering adverse reactions, such as anaphylaxis, simultaneously.

[0003]On the other hand, to the general immunity system, it is known that an antigen-specific unresponsive state, i.e., oral tolerance, will be derived at the same time the local immunity system centering on an intestinal mucosa is activated, when these antigenic substance is taken in on taking orally and an enteral target.

[0004]As application of this oral tolerance phenomenon, inhibition of the therapy of autoimmune diseases, such as rheumatism, and the rejection after an organ transplantation is tried. However, each of these trials applies the oral tolerance itself to a therapy.

Technical idea that it will use for pharmacotherapy does not exist.

EFFECT OF THE INVENTION

[Effect of the Invention]If this invention medicinal preparation is used, it can treat safely and effectively using the drug which was not able to be conventionally used for the therapy of the illness of the antigenicity, therefore Homo sapiens.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention]Therefore, although it has become clear that it has the drug effect conventionally outstanding by the animal experiment etc., the purpose of this invention, It is in providing a means to use effectively the drug which was not able to carry out clinical application for the antigenicity, or the drug with which the use was restricted even if clinical application was carried out as medicine.

MEANS

[Means for Solving the Problem]Then, if this invention person does not consider an oral tolerance phenomenon in the negative, but causes positively and medicates after an appropriate time with a protein nature drug etc. by injection when he inquires that an aforementioned problem should be solved, A general immunity response of anaphylaxis by this injection, etc. is not caused, but finds out that it can treat safely and effectively, and came to complete this invention.

[0007]Namely, medicinal preparation whose this invention is characterized by that what provides medicinal preparation comprises the following and which makes an active principle a drug which does a medicinal value so by internal use, and does a medicinal value so by ****** and injection substantially and, with which a medicinal value is no longer demonstrated by the repetition administration by injection.

This pharmaceutical preparation for drug content internal use that is sufficient administration number of unit to derive oral tolerance.

This pharmaceutical preparation for drug content injection for prescribing a medicine for the patient, after oral tolerance is derived.

[0008]Substantially, this invention does a medicinal value so by internal use, and does a medicinal value so by ****** and injection, And administer orally a drug with which a medicinal value is no longer demonstrated by repetition administration by injection, oral tolerance is made to derive, and a cure for a disease by this drug injecting subsequently is provided.

[0009]

[Embodiment of the Invention]The active principle which the medicinal preparation of this invention consists of pharmaceutical preparation for injection for making the pharmaceutical preparation for internal use and the medicinal value for deriving oral tolerance fundamentally reveal, and is contained in this pharmaceutical preparation for internal use and the pharmaceutical preparation for injection is the same drug. The drug used for the medicinal preparation of this this invention as an active principle is a drug with which a medicinal value is done so by internal use, and it does a medicinal value so by ****** and injection substantially, and a medicinal value is no longer demonstrated by the repetition administration by injection. It is not saying drug effect of the grade which a

medicinal value's is accepted that there is no **** by internal use, and is substantially accepted to be effective by internal use here not being shown, and not absorbed. The drug which may be absorbed to such an extent that there is **** about a medicinal value substantial with taking orally as such a drug as for nothing is preferred, and is a with a molecular weights of 3000 or more protein nature drug more preferably. Although the protein which has physiology activity, polypeptide, or sugar protein is mentioned as this drug, For example, cytokine, hormone, synthetic polypeptides, and synthetic sugar proteins, An antibody etc. are mentioned and neocarzinostatin, an insulin, interferon, a tumor necrosis factor (TNF), an epidermal growth factor (EGF), interleukin, erythropoietin, parathormone, opioid peptide, calcitonin, etc. are more specifically mentioned. As an antibody, the antibody for embellishing DDS, such as an antibody for a therapy (that from which itself becomes a drug), and liposome, is mentioned. As an antibody for a therapy, an immunosuppresant (organ-transplant-rejection inhibitors, such as Orthoclone OKT-3), An autoimmune disease treating agent, anticancer agents (anti-selectin antibody etc.) (anticancer Homo sapiens antibody etc.), infectious disease treating agents (Homo sapiens neutralizing antibody of HIV, etc.), the agents for cardiovascular disease (anti-blood platelet monoclonal antibody etc.), etc. are mentioned more concretely. As an antibody for embellishing DDS, the thing to the specific tissue and specific cells (for example, cancer cell) which are used for a missile therapy, etc. are mentioned concretely.

[0010]Like the above, the pharmaceutical preparation for internal use in the medicinal preparation of this invention is for making oral tolerance derive, and needs sufficient administration number of unit to derive oral tolerance. Here, 1 administration unit means a part prescribed a medicine for the patient once. And if the quantity of the drug blended into each administration unit is a quantity which does not do drug effect so substantially and in which derivation of an intestinal tract (membrane) immune system is made, it is enough. The administration number of unit should just be sufficient number to derive oral tolerance as a result of deriving a gut immunity system, for example, should just be 2-30.

[0011]An oral tolerance derivation adjuvant may be made to contain in this pharmaceutical preparation for internal use in addition to a drug. It cannot be overemphasized that the additive agent for a tablet, a granule, subtle granules, a capsule, syrups, a pill, etc. being mentioned, and considering it as these dosage forms as dosage forms of the pharmaceutical preparation for internal use, for example, an excipient, a binding material, disintegrator, lubricant, a coating agent, etc. can be added.

[0012]It is for prescribing the pharmaceutical preparation for injection in the medicinal preparation of this invention for the patient, after oral tolerance is derived, and on the

other hand, making drug effect reveal, and the administration number of unit should just be one or more. The loadings of the drug in the pharmaceutical preparation for injection are a quantity in which this drug reveals drug effect by injection.

[0013]As this pharmaceutical preparation for injection, the pharmaceutical preparation for intravascular injections, such as an intravenous injection and arterial injection, subcutaneous injection, or intramuscular injections is mentioned. as the dosage forms of these pharmaceutical preparation -- aquosity injections, oily suspension for injection, aquosity suspension for injection, emulsion injections, and business -- the time -- the powder restoration injections for preparation, freeze-drying injections, etc. -- mentioning -- having . In using these dosage forms, pH modifiers, such as chloride, phosphoric acid, and sodium hydroxide, Soothing agents, such as isotonizing agents, such as stabilizing agents, such as sodium hydrogen sulfite and sodium sulfite, sorbitol, mannitol, sodium chloride, potassium chloride, and glycerin, procaine hydrochloride, and phenol, etc. may be blended.

[0014]Although the medicinal preparation of this invention may supply separately said pharmaceutical preparation for internal use, and the pharmaceutical preparation for injection to a medical site, it is preferred to supply as combination pharmaceutical preparation (kit) which combined them.

[0015]The directions for the medicinal preparation of this invention are performed by prescribing the pharmaceutical preparation for internal use for the patient first, making oral tolerance derive, prescribing the pharmaceutical preparation for injection for the patient subsequently, and treating an object disease as above-mentioned.

EXAMPLE

[Example]Next, although working example is given and this invention is explained in detail, thereby, this invention is not restricted at all.

[0017]The ovalbumin of the molecular weight 45000 was used as reference example 1 model antigen. It omits the following OVA. First, in order to make a Wister system male rat (n= 11) activate a general immunity system, 2mg/ml of OVA solution was repeated to 0.5-ml intraperitoneal 3 times at intervals of 1 time or ten days, and it medicated it with it. Ten days after the last intraperitoneal injection, 0.1mg/ml of OVA solution [0.5 ml of] was prescribed for the patient into the vein, and both time transition of the serum concentration at that time and the antibody titer in a blood serum were measured by the ELISA method this time. In all the experiments, along with the same administration schedule, intraperitoneal was medicated only with the physiological saline which does not

contain OVA as contrast, and the comparative examination was always performed with the OVA administration group by making this into a control group.

[0018]Time transition of serum concentration when OVA is administered further intravenously is shown in the rat which repeated and medicated intraperitoneal with OVA solution at drawing 1 and drawing 2. In the rat which injected intraperitoneally once, the significant difference was not seen between control (drawing 1). On the other hand, when sensitization by intraperitoneal injection was performed 3 times, it became clear that the rat (high response group) in which prompt disappearance is shown out of whole body blood clearly lower than the early stages of administration as for the OVA concentration after intravenous injection exists among 11 animals in six animals and more than a moiety (drawing 2).

[0019]In these rats, as a result of a general immunity system's being activated by intraperitoneal repetition administration, to OVA, the antibody centering on IgG is produced and it is thought that this worked as a neutralizing antibody. This result suggests a possibility that the same change will take place in Homo sapiens, also when performing a long-term therapy using a actual protein nature drug.

[0020]The IgG level in a blood serum after the OVA sensitization was examined about the rat (low response group) as which a difference is not regarded by the blood drug concentration of OVA between control by 3 times of sensitization. As a result, the IgG level of the low response group rat was low generally, and the control group and the big difference were not seen.

[0021]Next, AUC was computed from blood-drug-concentration transition of OVA as an index of comparison with a sensitization group and a control group. By a quantity response group rat, it compares with control among the rats which carried out sensitization 3 times, It was decreasing remarkably with the abbreviation 1/3, the general immunity system was activated by repeating and prescribing a protein nature drug for the patient, and the result which points out a practical problem [say / that maintenance of the drug effect in a long-term therapy becomes difficult] was obtained (drawing 3).

[0022]working example 1 -- first, in order to derive oral tolerance, OVA solution was beforehand administered orally continuously for three days. Next, sensitization of the OVA solution was carried out 3 times to intraperitoneal at intervals of ten days like the reference example 1, and OVA was administered intravenously ten days after the last intraperitoneal injection. After deriving the immunological tolerance by internal use as a control group, the rat which medicated intraperitoneal with the physiological saline which does not contain OVA was produced.

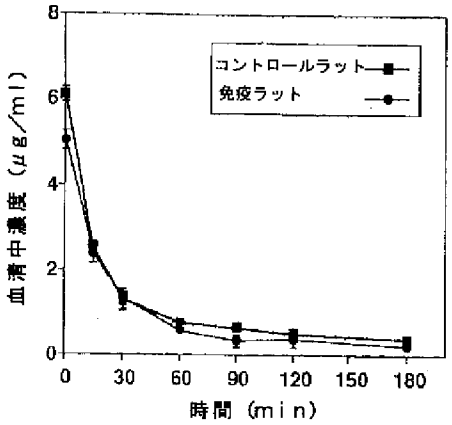
[0023]The examining result in the rat which medicated drawing 4 with OVA solution with a

concentration of 50mg/ml continuously for 1 ml and three days beforehand in taking orally is shown. When OVA was prescribed for the patient into a vein at the rat for which 3 times of sensitization were performed to intraperitoneal after administering orally so that clearly from drawing 4, as for the disappearance out of blood, compared with the control group, the difference was not seen at all. At this time, the rise significant to the antibody titer in a blood serum was not accepted, but it is deriving tolerance to general immunity by internal use of an antigenic substance, the antibody production after repetition administration was controlled, and it became clear that change of that moving state in the living body can be prevented (drawing 5). Therefore, also when actually performing the long-term therapy using a protein nature drug, it becomes maintainable [drug effect] by prescribing the medicinal preparation of this invention for the patient.

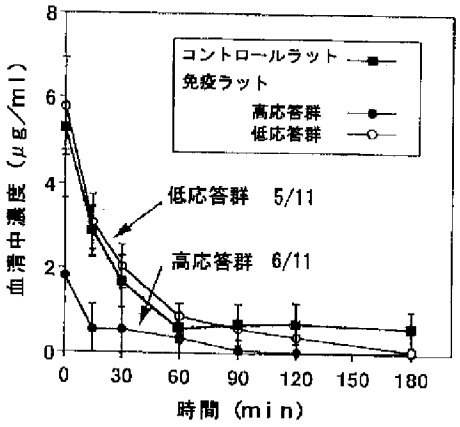
[0024]It examined like working example 1 except decreasing the amount of internal use of OVA for deriving working example 2 oral tolerance to 5 mg. As a result, as shown in drawing 6 and drawing 7, also when a difference was not observed in the blood drug concentration after OVA intravenous injection between control but a dose was reduced to 1/10 compared with working example 1, it was shown that oral tolerance is derived enough.

DRAWINGS

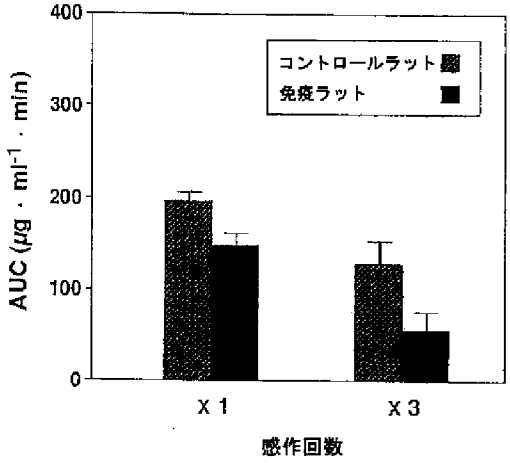
[Drawing 1]



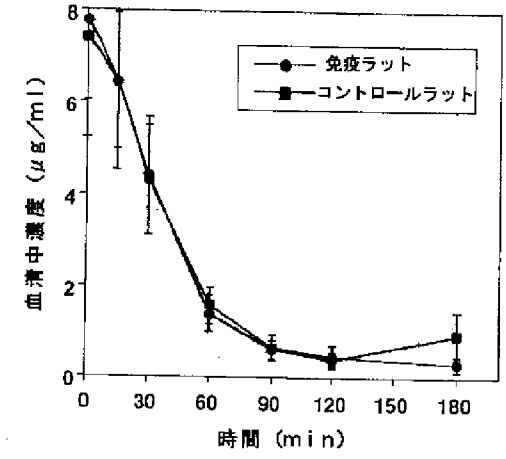
[Drawing 2]



[Drawing 3]



[Drawing 4]



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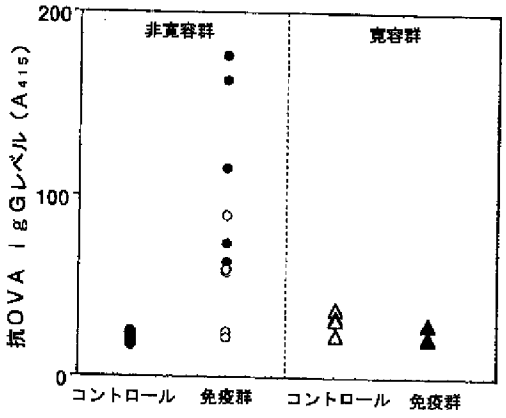
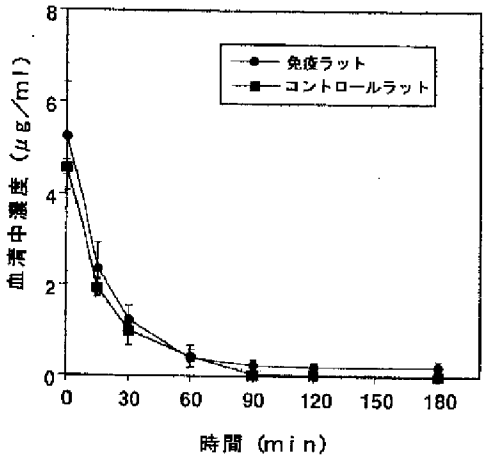


[Drawing 6]



[Drawing 7]